Gestational Trophoblastic Disease

UCSF Obstetrics & Gynecology Update: What does the evidence tell us?

Jocelyn S. Chapman, MD
Assistant Professor
Gynecologic Oncology
Obstetrics, Gynecology & Reproductive Sciences
October 20, 2017

No financial disclosures

Objectives

I. Epidemiology, definitions and terminology

I. Review the clinical entity of gestational trophoblastic neoplasia and discuss the spectrum of presentation

I. Discuss clinical pearls for work-up and evaluation

I. Review the pitfalls in staging and management

Scope of the problem

I. Incidence of molar pregnancy
   - 1-2/1,000 pregnancies
   - Racial and ethnic differences unclear

I. Incidence of choriocarcinoma
   - 1/40,000 pregnancies and 1/40 moles (Europe and N. America).
   - 9/40,000 pregnancies and 3/40 moles (Southeast Asia and Japan)

I. Incidence appears to have declined over the past 30 years in all populations.
Risk Factors for Complete Hydatidiform Mole

1. Extremes of maternal age (1.9 times higher than reference)
2. Prior molar pregnancy (10-20 times higher than reference)
3. History of SAB (2-3 fold higher than reference)

Risk Factors for Choriocarcinoma

1. Prior complete hydatidiform mole (1,000 times more likely than reference)
2. Asian, American Indian and African American ethnicities (?)

Where does this disease start?

4 GTDs and 3 GTNs

- Hydatiform mole
  - Complete (15-20% risk of GTN)
  - Partial (1-5% risk of GTN)
- Invasive mole
- Choriocarcinoma
- Placental site trophoblastic tumor (PSTT)
Clinical & pathologic features of GTD

<table>
<thead>
<tr>
<th>Classification</th>
<th>Pathology</th>
<th>Usual karyotype</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial hydatidiform mole</td>
<td>Fetal hydropidema of all Genits</td>
<td>69,000: two paternal haploid sets and one maternal haploid set</td>
<td>Difficult to diagnose on ultrasound as a fetus can be present during the first 6-10 weeks. Most present as failed pregnancies. Less than 1% require additional treatment after evacuation</td>
</tr>
<tr>
<td>Complete hydatidiform mole</td>
<td>Generalized trophoblastic Benign</td>
<td>46,XX: two haploid sets, both paternal (heterozygous diploid)</td>
<td>Uterine cavity filled with vascular mole tissue on ultrasound without an embryo. Approximately 10-15% become malignant and require additional therapy</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mole</td>
<td>Features of invasion</td>
<td>Virtually all are anaplastic and diploid</td>
<td>Molar tissue invading the myometrium and may cause uterine rupture if not treated</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td><em>Histologically differentiated from a hydatidiform mole</em></td>
<td>Contains maternal and paternal chromosomes (uterine choriocarcinoma of chorion origin)</td>
<td>Most follow a live birth, stillbirth, miscarriage or ectopic pregnancy, but can arise from a hydatidiform mole. There is frequently metastatic spread. Highly curable with chemotherapy</td>
</tr>
<tr>
<td>Recurrent site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation site tumor (PSTT)</td>
<td></td>
<td>Contains maternal and paternal chromosomes</td>
<td>Slow-growing malignancy. Invades the myometrium and potentially metastasizing to the lung. CGC levels are less elevated than in choriocarcinoma. Usually treated with surgery and chemotherapy</td>
</tr>
</tbody>
</table>

Human chorionic gonadotropin (HCG)

Partial versus complete moles

6 Types of hCG in serum
The problem of phantom hCG

<table>
<thead>
<tr>
<th>Case</th>
<th>Time period from evacuation</th>
<th>Limit of variable hCG values over time period</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 year</td>
<td>13 - 40 E.U/L</td>
<td>Mtx, APL, MPX, MBC, EMACO</td>
</tr>
<tr>
<td>2</td>
<td>7 year</td>
<td>11 - 75 E.U/L</td>
<td>Mtx, APL, MBC, EMACO</td>
</tr>
<tr>
<td>3</td>
<td>3 year</td>
<td>11 - 24 E.U/L</td>
<td>Mtx, APL, MPX, MBC, APLNT</td>
</tr>
<tr>
<td>4</td>
<td>4 year</td>
<td>17 - 198 E.U/L, 30 b/s, b</td>
<td>Mtx, Mtx, Mtx, MBC, Mtx</td>
</tr>
<tr>
<td>5</td>
<td>2 year</td>
<td>44 - 198 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>6</td>
<td>2 year</td>
<td>35 - 90 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>7</td>
<td>2 year</td>
<td>17 - 180 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>8</td>
<td>4 year</td>
<td>5 - 10 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>9</td>
<td>2 year</td>
<td>17 - 140 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>10</td>
<td>2 year</td>
<td>17 - 80 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>11</td>
<td>2 year</td>
<td>17 - 500 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>12</td>
<td>3 year</td>
<td>17 - 30 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>13</td>
<td>2 year</td>
<td>17 - 25 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>14</td>
<td>2 year</td>
<td>17 - 25 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>15</td>
<td>1 year</td>
<td>17 - 10 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>16</td>
<td>2 year</td>
<td>17 - 10 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>17</td>
<td>2 year</td>
<td>17 - 10 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>18</td>
<td>2 year</td>
<td>17 - 10 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>19</td>
<td>1 year</td>
<td>17 - 10 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
<tr>
<td>20</td>
<td>&lt;6 months</td>
<td>17 - 10 E.U/L</td>
<td>Mtx, APL, MPX, EMACO</td>
</tr>
</tbody>
</table>

Three ways to rule out phantom HCG

I. Run the serum HCG assay on a urine specimen.
   - Antibodies are filtered out in urine

I. Request serial dilution.
   - If there is true GTN then serial dilution should result in a parallel decrease in HCG.
   - If the HCG result is a false positive, serial dilution should NOT show a parallel decrease with dilution.

III. Send urine and blood to the USA hCG Reference laboratory (hcglab.com).

How to diagnose post-molar GTN?

I. hCG plateau for 4 consecutive values over 3 weeks

II. hCG rise of >/= 10% for 3 values over 2 weeks

III. hCG persistence 6 months after molar evacuation

IV. Histopathologic diagnosis of choriocarcinoma

V. Presence of metastatic disease

Include the following in your work-up for GTN

I. Complete history and examination

II. CBC, coags, chemistries, LFTs, TFTs, blood type, Rh status, quantitative hCG
   - Rhogam?

III. Imaging: CXR and ultrasound
   - CT abdomen and pelvis
   - CT chest if CXR negative
   - Brain imaging if there are chest mets
Don’t forget these things when taking a suspected GTN case to the OR.

I. Uterotonic
II. 12-14mm canula
   – Start at the internal cervix
   – Ultrasound guidance
III. Type and Cross
IV. Can consider hysterectomy
   – Completed childbearing
   – Decreases risk for local persistent disease
   – Treatment of choice for PSTT.
   – Risk of post-molar GTN 3-5% so must have surveillance.

Staging GTN

<table>
<thead>
<tr>
<th>Stage</th>
<th>Decision</th>
<th>Risk factor</th>
<th>Score</th>
<th>Age</th>
<th>Pregnancy</th>
<th>Prior history</th>
<th>Prior interventions</th>
<th>Length of tumor (cm)</th>
<th>Number of metastases</th>
<th>Prior failed chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>GTE extends bilaterally on the external iliac arteries</td>
<td>≤50</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10 cm</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>GTE extends bilaterally on the external iliac arteries</td>
<td>≤50</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10 cm</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>All other metastatic sites</td>
<td>≤50</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10 cm</td>
<td>3</td>
</tr>
</tbody>
</table>

Treatment of Choriocarcinoma

- Low-risk: prognostic score <7
  - Methotrexate (MTX) +/- leucovorin rescue
    - Weekly IM MTX (30-50mg/m2) easiest dosing and lowest side effects but higher failure rates.
    - MTX 0.4mg/m2 IM/IV daily for 5 days every 2 weeks is most effective.
  - Actinomycin-D (ACT-D)
- High-risk: prognostic score ≥7
  - EMA/CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine
  - MAC: MTX, ACT-D, cyclophosphamide
- These tumors are VERY chemo-sensitive!
Chemotherapy works!

Follow-up

- Check hCG monthly x 12 months
  - Risk of relapse in the first year is 3%
  - Risk of relapse after the first year is exceedingly low

- Oral contraceptives
  - Suppresses LH

- Subsequent pregnancy
  - 1-2% risk of 2nd GTN event
  - Pelvic U/S in 1st trimester
  - Placenta goes to pathology
  - Check bHCG 6 weeks after delivery

Subsequent Pregnancy Outcome

<table>
<thead>
<tr>
<th>Prior Molar pregnancy</th>
<th>Complete</th>
<th>Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pregnancies</td>
<td>1254</td>
<td>218</td>
</tr>
<tr>
<td>Total deliveries</td>
<td>962</td>
<td>167</td>
</tr>
<tr>
<td>Term</td>
<td>68.7%</td>
<td>74.3%</td>
</tr>
<tr>
<td>Preterm</td>
<td>7.4%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

| Spontaneous abortion  | 17.8%    | 16.1%   |
| Elective abortion     | 3.2%     | 5.0%    |
| Ectopic               | 0.9%     | 0.5%    |

| Repeat Mole           | 1.4%     | 1.8%    |

Garner, Contemp Obstet Gynecol 2001

A Case

- 16 wks GA
- Presents with: abdominal pain, n/v, headache
- U/S consistent with molar pregnancy
- bHCG 400,000
Conclusions

- GTN is curable
- Think about the possibility of phantom hCG
- Don’t forget your OR checklist
- Call your friendly Gyn-Oncologist to help with management and treatment
- Remember the principles of follow-up & counseling for future conceptions.

Question #1
TRUE OR FALSE: Partial moles are more likely than complete moles to progress to GTN.

A. True  B. False

FALSE

Question #2
Which of the following is TRUE when taking a patient with a suspected molar pregnancy for D&C?

A. A type and screen is sufficient for pre-op laboratory evaluation.
B. Sharp curettage is better than suction curettage.
C. Uterotonics should be available.

4%  90%
Question #3

TRUE OR FALSE: A patient with a persistent bHCG between 40 - 60 IUs/L, normal menses and no evidence of GTD on imaging should be given methotrexate.

A. True
B. False

FALSE

Questions?